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The Essential Trace Elements

Walter Mertz

Summary. Essential trace elements are required by man in amounts ranging from 50 micrograms to 18 milligrams per day. Acting as catalytic or structural components of larger molecules, they have specific functions and are indispensable for life. Research during the past quarter of a century has identified as essential six trace elements whose functions were previously unknown. In addition to the long-known deficiencies of iron and iodine, signs of deficiency for chromium, copper, zinc, and selenium have been identified in free-living populations. Four trace elements were proved to be essential for two or more animal species during the past decade alone. Marginal or severe trace element imbalances can be considered risk factors for several diseases of public health importance, but proof of cause and effect relationships will depend on a more complete understanding of basic mechanisms of action and on better analytical procedures and functional tests to determine marginal trace element status in man.

The bulk of living matter consists of hydrogen, carbon, nitrogen, oxygen, and sulfur. The concentrations of these elements in biological matter can be expressed in grams per kilogram; they are required in gram amounts per day in humans. The macrominerals sodium, magnesium, phosphorus, chlorine, potassium, and calcium serve as structural components of tissues, as constituents of the body fluids, and are essential for the function of all cells. Their concentrations in living tissue and the adult human requirement are somewhat lower than those of the bulk elements, but still can be expressed as grams per kilogram and grams or fractions of a gram per day. The remaining elements of the periodic system occur in the organism in much lower concentrations and are expressed in terms of milligrams or micrograms per kilogram of tissue. Such concentrations were not easily quantified by the early analytical methods, hence the name "trace" elements (*1*).

Trace elements, which include all the naturally occurring elements in the periodic system except the bulk elements and macrominerals, are best classified in two categories: those elements whose essentiality has been established by accepted scientific standards and those for which proof of essentiality does not exist. Research during the past three decades has added molybdenum, selenium, chromium, nickel, vanadium, silicon, and arsenic to the list of essential elements. This suggests that additional elements could be proved essential by future research and the number of elements now accepted as essential should not be considered final.

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Essentiality, Dose, and Response

By the simplest definition, an essential element is one required for maintenance of life; its absence results in death of the organism. Severe deficiencies of an element that result in death are difficult to produce, particularly if the element is required in very low concentrations. A broader definition of essential elements has therefore been proposed and is widely accepted: An element is essential when a deficient intake consistently results in an impairment of a function from optimal to suboptimal and when supplementation with physiological levels of this element, but not of others, prevents or cures this impairment (*2*). Essentiality is generally acknowledged when it has been demonstrated by more than one independent investigator and in more than one animal species. By these criteria, the following trace elements are now considered essential in animals: silicon, vanadium, chromium, manganese, iron, cobalt, nickel, copper, zinc, arsenic, selenium, molybdenum, and iodine. Growth depression resulting from deficiency of fluorine and tin and growth stimulation following supplementation with these elements have been reported (*3*), but not yet confirmed. Nevertheless, fluorine can be considered essential on the basis of its demonstrated effect on dental health (*4*) (Fig. 1).

The degree to which a function is impaired in an animal with a deficiency is not related to the criterion of essentiality but depends on the degree to which

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exposure of the test animal to the trace element—by way of diet, water, and air—can be controlled. Such control is easy for elements that are required in relatively high concentrations, such as iron and zinc, but is difficult and requires special precautions for those that are required in much smaller concentrations, such as selenium, chromium, vanadium, nickel, and arsenic. The discovery of essential functions for trace elements during the past decade was possible only because the development of the "ultra-clean environment" made possible the maximum exclusion of contaminants (*5*).

The dependence of the severity of signs and of the effects of resupplementation on the degree of deficiency was formulated mathematically by Bertrand at the beginning of this century (*6*). As illustrated in Fig. 2, Bertrand's rule states that a function for which a nutrient is essential is very low or absent in a theoretical, absolute deficiency, and increases with increasing exposure to the essential nutrient. This increase is followed by a plateau representing the maintenance of optimal function through homeostatic regulation, and a decline of the function toward zero as the regulatory mechanisms are overcome by increasing concentrations that become toxic. Although each essential nutrient has its own specific curve which differs from that of other nutrients (for example, by the width of the plateau), the principle of Bertrand's model is probably applicable to all essential nutrients, including the bulk elements, water, and oxygen, as well as the individual trace elements. Two conclusions from this model are relevant to the understanding of trace element research: (i) for each element there is a range of safe and adequate exposures, within which homeostasis is able to maintain optimal tissue concentrations and functions; and (ii) every trace element is potentially toxic when the range of safe and adequate exposure is exceeded.

Past trace element research has demonstrated essential functions for at least three trace elements, selenium (*7*), chromium (*8*), and arsenic (*9*), which previously had been known only as toxic. These examples have important implications for the quality of the environment and for present efforts to reduce exposure to "toxic" elements to a minimum. Although adequacy of trace element metabolism is strongly influenced by a multitude of dietary interactions (*10*), safe and adequate intakes are reasonably well defined for iron, zinc, and iodine. Ranges have been estimated for fluorine, chromium, manganese, copper, selenium, and molybdenum, but are unknown for the "new" trace elements, vanadium, nickel, silicon, and arsenic (*11*). Table 1 presents the recommendations of the Food and Nutrition Board of the National Academy of Sciences for nine trace elements.

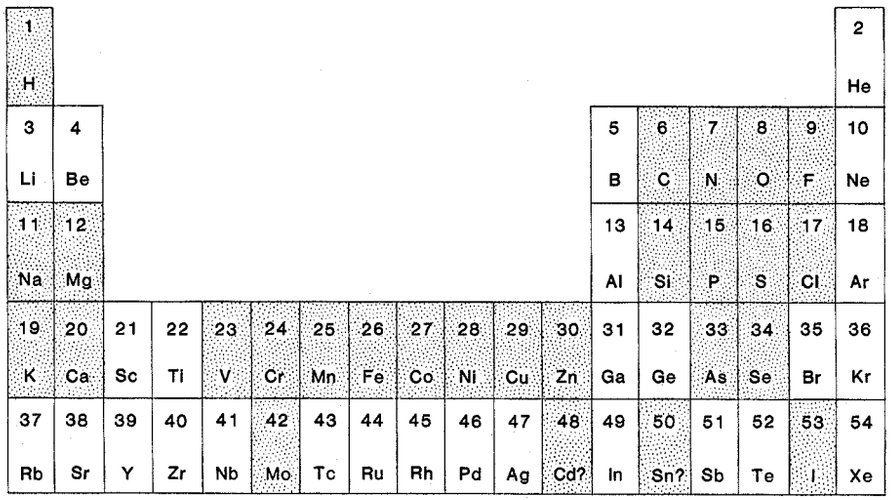

Fig. 1. Part of the Periodic Table showing all elements accepted as essential (shaded). Question marks indicate unconfirmed reports of growth stimulation.

The Basis of Trace Element Action

In an adult human, the daily turnover of cobalt as a constituent of vitamin B_{12} is between 100 and 150 nanograms per day, corresponding to approximately 2 parts per trillion of the adult body weight; the average vitamin B_{12}–cobalt concentration in blood approximates 5 ng/liter. Deficiency of vitamin B_{12} results in a serious disease, pernicious anemia. Although other trace elements, such as iron, copper, and zinc are present in the organism in much higher concentrations, the example of cobalt challenges the scientist to explain how small traces of an element profoundly influence functions that are essential for health, and how they are recognized by the organism and transported to their ultimate site of action. Our knowledge of the chain of events linking the ionic property of a trace element to the expression of a health-related function in the whole organism is incomplete, but some parts of this sequence can be discussed.

Amplification. All known essential trace elements are constituents of or interact with larger molecules, such as enzymes or hormones, that, in turn, regulate much larger masses of substrate. If this substrate itself has some regulatory function, the effects are further amplified to a degree that could relate to the overall effect of the trace element in the intact organism (Fig. 3).

Specificity. The effects of trace elements in vivo are absolutely specific: A deficiency of one element can be pre-

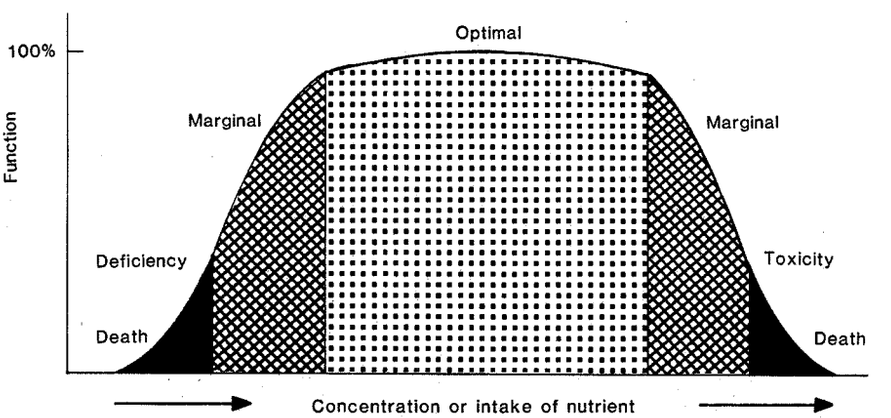

Fig. 2. Dependence of biological function on tissue concentration on intake of a nutrient.

vented and remedied only by that, but not by another, element, even if the latter is chemically related to the first. If anything, the severity of the deficiency is aggravated by excesses of chemically similar elements. For example, molybdenum deficiency is not easily produced by molybdenum-deficient diets alone, but can be provoked by adding to the diet excessive concentrations of the closely related trace element tungsten (*12*). This specificity of trace element action in vivo contrasts with the much less specific behavior of trace elements in vitro. It is known that in at least two metalloenzymes the specific element zinc can be replaced in vitro by other transition metals, such as cadmium and cobalt, with little loss of overall enzyme activity but with a change of the enzyme's affinity for substrates (*13*). Enzymes that do not contain a trace element as an integral part but are activated by metals, respond to in vitro addition of several transition elements with a dose-dependent activation (*14*). This suggests that the high degree of specificity in vivo is brought about by carriers with specific sites that recognize a certain element when it enters the organism and deliver it to its own sites of action, but not to others. The mechanisms that govern the association of an element to its carrier and its subsequent dissociation to its site of action are not known. Among the large carrier molecules are plasma proteins, such as transferrin, ceruloplasmin, albumin, α-macroglobulin, transmanganin, and nickeloplasmin. In addition, a fraction of the trace elements in serum is carried in the form of amino acid or small peptide complexes (*15*). The binding capacity of specific protein carriers is usually undersaturated. Under normal conditions, for example, transferrin carries only one-third of its maximum iron load. The reserve binding capacity can be considered an effective buffer against excessive exposures; toxicity from nonspecific organ distribution of trace elements usually results only after this buffering capacity is exceeded.

The carrier substances assure the delivery of trace elements to their specific sites of action. At these sites, the action of a trace element is specific and is dependent on properties such as valence state, redox potential, ionic radius, coordination number, coordination geometry, spin state (high versus low spin transition), and rate of ligand exchange. These properties, in their entirety, clearly distinguish one element from another. Although the influence of many of these individual parameters on biological action is not completely understood, it can be stated that the property of trace elements, particularly those that are transition elements, to form coordinate compounds is the chemical basis of their biological action.

Table 1. Recommended safe and adequate dietary intakes for adults. [From (*11*)]

Element	Intake (mg/day)
Iron (males)	10
Iron (females)	18
Zinc	15
Manganese	2.5 to 5.0
Fluorine	1.5 to 4.0
Copper	2.0 to 3.0
Molybdenum	0.15 to 0.5
Chromium	0.05 to 0.2
Selenium	0.05 to 0.2
Iodine	0.15

Homeostatic regulation. The organism has powerful mechanisms that maintain the plateau of optimal function in the biological dose-response curve throughout a wide range of dietary and environmental exposure. For example, dietary intakes of selenium that are compatible with good health vary from around 30 μg/day (Finland and New Zealand) to more than 300 μg/day (Venezuela), a range of 1 to 10 or more (*16*). Comparable extremes of some macronutrients, such as water, salt, or protein over extended periods of time would be incompatible with health. One aspect of homeostasis already has been discussed: The specific carrier substances of trace elements are normally less than fully saturated and thus present a certain buffering capacity against excesses, but control of absorption or excretion mechanisms, or both, is quantitatively more important.

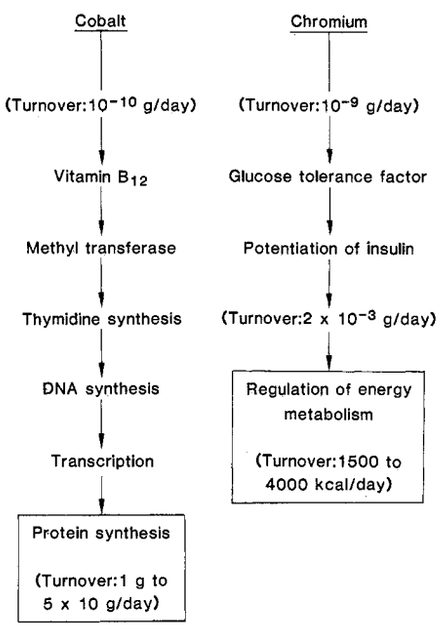

Fig. 3. Amplification of trace element action.

Gastrointestinal absorption of trace elements occurs in three different phases: (i) the intraluminal phase with its chemical reactions and interactions of trace elements in stomach and intestines; (ii) the translocation phase, that is, diffusion or transport of the element across the cell membrane of the epithelial lining; and (iii) the mobilization phase, including mobilization and transport of the intracellular elements into the blood stream or their sequestration back into the intestinal lumen. The chemical reactions during the intraluminar phase are dominated by the *p*H of the luminal contents and by the composition of the food entering the stomach. Small anionic elements such as fluorides, selenites, and iodides are not much influenced by either *p*H or dietary composition and are absorbed quite freely, whereas the cationic forms of the transition elements are highly dependent on both influences. These cations, while freely soluble in the acidic *p*H of the stomach contents, would form insoluble hydroxides in the alkaline *p*H of the intestines and become unavailable for absorption unless protected by ligands that successfully compete with hydroxyl ions (*17*). Thus, the nature of the ligands that form coordination or chelate compounds with the elements is an important determinant of bioavailability. Such coordinate compounds or chelates may be present in the diet and absorbed into the epithelial cell unchanged, as is the case for the heme iron complex. Alternatively, they may be hydrolyzed in the acidic milieu of the stomach and give way to new associations with dietary or secreted substances having greater affinity to the metal involved. Amino acids and other organic acids and sugars and their derivatives are examples of important ligands. It is not known whether the metal complexes or chelates are absorbed intact or whether they are dissociated at the cell surface prior to the absorption of the metal.

The second phase, translocation across the cell membrane, may be a simple diffusion for small anions but is facilitated diffusion or active transport for most of the cationic elements. Both of these two last mechanisms are saturable: The relative rate of transport decreases with increasing concentration, and this is one important aspect of regulating absorption. For at least one macroelement, calcium, a direct hormonal

regulation of the active transport phase of intestinal absorption has been demonstrated (*18*); it is not known whether such regulation also determines the active transport of the trace elements.

The events within the intestinal epithelial cells are not well known in general, but specific mechanisms have been postulated for two trace elements, iron and zinc. These elements, once absorbed into the cell, are bound to specific storage proteins, ferritin and metallothionein, respectively. Thus, depending on the relative concentration of these proteins and of the entering ions and on the equilibrium constants, a variable proportion of the absorbed elements remains free for further reactions that initiate mobilization into the general circulation. If the concentration of the binding proteins is relatively high, a greater proportion of the entering ions is bound, and a proportionally smaller part of the absorbed elements is available for transport into the circulation. As the epithelial cells are replaced by younger cells and sequestered into the intestinal lumen, the storage proteins and the elements bound to them are lost to the organism and become part of the intestinal content. It is known that the concentration of metallothionein in organs can be increased by administration of the trace elements that they specifically bind. On this basis, a feedback mechanism regulating zinc absorption has been postulated: increasing concentrations of zinc in the plasma stimulate increased metallothionein synthesis in the intestinal cells, which leads to a greater trapping of absorbed zinc and eventual loss by desquamation and a relative decrease of the functional supply to the organism. As the plasma zinc concentration declines, the stimulus for metallothionein synthesis diminishes, and the portion of absorbed zinc available for transport into the circulation is correspondingly increased (*19*). Mechanisms of this nature may be the predominant regulators of homeostasis for iron, zinc, copper, and possibly other elements, for which regulation by urinary excretion is relatively insignificant.

The major routes of excretion of trace elements are intestines and kidneys; losses of trace elements via skin and its appendices, and sweat and breath also can become important in hot climates and, for selenium, during overexposure. These excretory routes, however, are slightly or not at all subject to homeostatic regulation. For small anions, such as fluorides and iodides, and for selenium and chromium, urine accounts for nearly all the turnover. Excessive intakes of these elements are effectively excreted by the kidney, whereas the homeostasis of manganese is predominantly regulated by control of excretion into the intestines. The physiological and biochemical mechanisms that govern homeostasis by regulation of excretion are not known but, with normal kidney function, protein-bound trace elements are not removed and excretion is limited to small molecular species. The relative distribution of elements between these two categories of ligands is, however, not the only or predominant factor; tubular reabsorption plays an important role for at least some trace elements that are filtered at the glomerulus as constituents of low molecular weight compounds.

Trace Element Deficiencies in Man and Animals

Much information about deficiency signs and their consequences has been amassed for animal species and man (*20*) (Table 2). Here I describe only the present state of nutritional trace element research by discussing three elements that can serve as examples of three stages of progress: The first stage is based on decades of research and centuries of empirical knowledge (iodine); the second is based on more recent history and presents many unanswered questions (chromium); the third is based on only a few years of study of the "new" trace elements for which nutritional importance was discovered during the past decade (silicon).

Iodine. Although the first convincing association between iodine and thyroid function was established 130 years ago (*21*), sources of iodine, such as burnt sponges, were used for many centuries as an effective treatment for goiter. The only known function of iodine is as the active component of the thyroid hormones triiodothyronine and thyroxine. The mechanism of synthesis of these hormones is known. There is no understanding yet, however, of why the addition of three or four iodine molecules transforms a biologically inert compound, thyronine, into a powerful hormone that controls energy metabolism in all species, biological transformation in Amphibia, and even mental attitudes and intellectual performance in man. In spite of the wide distribution of iodine throughout the organism, especially in the ovaries, no extrathyroidal functions for this element have been established. However, iodine deficiency per se, regardless of thyroid function, is associated in experimental animals with dysplasia of the mammary gland that responds to supplementation with inorganic iodine, but not with thyroid hormones (*22*).

The iodine status of animals and man is strongly dependent on iodine concentrations in soil, water, and air. Although this environmental influence is modified by interactions with goitrogens that interfere with the utilization of iodine and by interactions with several trace elements, the worldwide maps of goiter incidence in populations are generally superimposable on those delineating low iodine concentrations in soils. Public health measures of increasing the iodine intake in deficient areas through fortification of table salt or bread have been effective, when properly designed and executed, as shown by the substantial reduction in goiter incidence in the "goiter belt" of the United States. Yet, iodine deficiency remains a problem, affecting hundreds of millions of people worldwide. This may be due to insufficient levels of iodization of carrier substances that fail to furnish the estimated requirement of 75 to 150 μg/day (*11*), or it may be due to logistical difficulties in developing countries or to food laws prohibiting the addition of iodine.

In the United States, approximately half of the table salt for household consumption is enriched with 100 μg/g. This iodized salt, which is clearly marked, has substantially reduced, but not totally eliminated, the incidence of goiter in this country. A number of cases of "residual" goiter were recognized in recent health and nutrition surveys; these are not related to an insufficient iodine intake, but possibly to goitrogens (*23*). A second development that contributed to the increased iodine intake of the U.S. population was the use of iodine compounds for reasons not related to nutritional needs. Iodine-containing disinfectants used in the dairy industry, iodates used in parts of the baking industry, and iodine-containing coloring agents have substantially contributed to the average iodine intake in the United States that is now estimated at several times the recommended dietary allowance of 150 μg/day. The Food and Nutrition Board of the National Academy of Sciences addressed this situation with the following statement: "Although the present iodine intake in the United States can be considered safe, any additional increases should be viewed with concern. It is recommended that the many adventitious sources of iodine in the American food system, such as iodophores in the

Table 2. Classification of the essential trace elements.

Element	Function	Deficiency signs		Occurrence of imbalances in humans
		Animals	Humans	
Fluorine	Structure of teeth, possibly of bones; possibly growth effect	Caries; possibly growth depression	Increased incidence of caries; possibly risk factor for osteoporosis	Deficiency and excess known
Silicon	Calcification; possibly function in connective tissue	Growth depression; bone deformities	Not known	Not known
Vanadium	Not known	Growth depression, change of lipid metabolism, impairment of reproduction	Not known	Not known
Chromium	Potentiation of insulin	Relative insulin resistance	Relative insulin resistance, impaired glucose tolerance, elevated serum lipids	Deficiency known in malnutrition, aging, total parenteral alimentation
Manganese	Mucopolysaccharides metabolism, superoxide dismutase	Growth depression, bone deformities, β-cell degeneration	Not known	Deficiency not known; toxicity by inhalation
Iron	Oxygen, electron transport	Anemia, growth retardation	Anemia	Deficiencies widespread; excesses dangerous in hemochromatosis; acute poisoning
Cobalt	As part of vitamin B_{12}	Anemia; growth retardation in ruminant species	Only as vitamin B_{12} deficiency	Inability to absorb vitamin B_{12}; low B_{12} intake from vegetarian diets
Nickel	Interaction with iron absorption	Growth depression, anemia, ultrastructural changes in liver; impaired reproduction	Not known	Not known
Copper	Oxidative enzymes; interaction with iron; cross-linking of elastin	Anemia, rupture of large vessels, disturbances of ossification	Anemia, changes of ossification; possibly elevated serum cholesterol	Deficiencies in malnutrition, total parenteral alimentation
Zinc	Numerous enzymes involved in energy metabolism and in transcription and translation	Failure to eat, severe growth depression, skin lesions, sexual immaturity	Growth depression, sexual immaturity, skin lesions, depression of immunocompetence, change of taste acuity	Deficiencies in Iran, Egypt, in total parenteral nutrition, genetic diseases, traumatic stress
Arsenic	Not known	Impairment of growth, reproduction; sudden heart death in third generation lactating goats	Not known	Not known
Selenium	Glutathione peroxidase; interaction with heavy metals	Different, depending on species: muscle degeneration (ruminants), pancreas atrophy (chicken)	Endemic cardiomyopathy (Keshan disease) conditioned by selenium deficiency	Deficiency and excess in areas of China; one case resulting from total parenteral alimentation
Molybdenum	Xanthine, aldehyde, sulfide oxidases	Difficult to produce; growth depression	Not known	Excessive exposure in parts of Soviet Union associated with goutlike syndrome
Iodine	Constituent of thyroid hormones	Goiter, depression of thyroid function	Goiter, depression of thyroid function, cretinism	Deficiencies widespread; excessive intakes may lead to thyrotoxicosis

dairy industry, alginates, coloring dyes and dough conditioners, be replaced wherever possible by compounds containing less or no iodine'' (*11*).

The nutritional importance of iron also has been studied for decades. Although iron and iodine differ in many aspects of nutrition, metabolism, and deficiency, the following conclusions apply to both elements:

1) Deficiency results in serious disease in man and animals; toxicity is known for both but is not as great a health problem as deficiency.

2) Deficiencies affect hundreds of millions of people, and geographical problem areas are known. Individual supplementation is effective in preventing deficiencies. Public health measures of iodization have been proved effective. Substantial reduction of the goiter incidence is scientifically feasible; it depends on political decisions and economic considerations.

Chromium. The essential function of chromium for maintenance of normal glucose tolerance in rats was established in 1959 (*24*). This discovery was based on observations of impaired glucose tolerance in rats raised on purified diets that were complete with regard to all essential nutrients known at that time. The impairment of glucose tolerance was prevented by certain feed ingredients, such as brewer's yeast, and was cured by one dose of concentrates from brewer's yeast or kidney powder. After 5 years of purification and fractionation, the active ingredient was identified as trivalent chromium, which, in microgram quantities and in the form of certain inorganic complexes, prevented and cured the impairment of glucose tolerance in the experimental animals. Inorganic chromium compounds, added in vitro to epididymal fat tissue of chromium-deficient rats and Krebs-Ringer phosphate medium containing glucose, stimulated glucose uptake from the medium, but only in the presence of insulin. Utilization of glucose for oxidation and fat synthesis was equally affected by chromium, as was the transport across the cell membranes of D-galactose, a sugar that is not further metabolized within the fat cell.

These experiments suggested that chromium acted at the first step of sugar metabolism, cell transport, where insulin also exerts its primary action. Further studies in vitro and in vivo demonstrated that general insulin resistance was a consequence of chromium deficiency that could be prevented and cured by chromium administration. The fact that chromium is ineffective in the absence of insu-

lin, and its demonstrated effect in vitro to increase the slope of the insulin dose response of chromium-deficient tissue, indicated that chromium is not an insulin-like agent but a true potentiator of the hormone (*25*). Pronounced chromium deficiency produced in an environment that allows exclusion of trace element contamination resulted in a diabetes-like syndrome in rats, with fasting hyperglycemia, glycosuria, elevated serum cholesterol, and a high incidence of fat deposits in the aorta (*26*).

Chromium deficiency in human subjects cannot yet be reliably diagnosed by chromium analysis of body fluids or tissues. Its recognition depends on retrospective diagnosis: insulin resistance, manifested by impaired glucose tolerance in the presence of normal or even elevated concentrations of insulin, that is normalized by supplementation with physiological amounts of chromium. Two carefully controlled clinical cases of total parenteral nutrition have been reported independently (the patients had been sustained exclusively by administration of intravenous fluids). Both patients developed glucose intolerance, insulin resistance, and disorders of the central or peripheral nervous system, all of which were normalized after chromium, but not after insulin, administration (*27, 28*). Chromium-responsive impairment of glucose tolerance has also been reported in a large proportion of malnourished children studied in Jordan, Nigeria, and Turkey, but not in Egypt. Studies in the United States on middle-aged and elderly subjects with impaired glucose tolerance generally detected an improvement in one-third to one-half of the subjects, after chromium supplementation (*25*). A series of more recent studies demonstrated a significant reduction of total serum cholesterol in human subjects who were supplemented either with inorganic chromium or high-chromium brewer's yeast preparations. There was a strong lowering of the low-density lipoprotein cholesterol, with a simultaneous increase of the high-density lipoprotein cholesterol (*29–32*).

The daily human requirement for chromium has been estimated at 50 to 200 μg/day (*11*). This "range of safe and adequate intakes" is not always supplied by diets habitually consumed in the United States, in countries with low-chromium soils such as Finland, and in countries with basic problems of malnutrition.

Without a reliable diagnostic test for chromium status, the incidence and severity of chromium deficiency cannot be evaluated. Yet, chromium deficiency can be implicated as a significant risk factor for cardiovascular disease on the basis of animal studies and epidemiological as well as clinical correlations in human subjects (*26*).

Chromium was discussed in some detail as representative of the second stage of progress of trace element research, that is also representative for copper, zinc, and selenium. Although modes of action and signs of deficiency differ among these elements, several nutritional aspects are common to all and can be discussed together.

1) Serious deficiencies in human subjects have been described; those of zinc in Iran and of selenium in China are of considerable public health importance. The signs of deficiency are compatible with the known mechanisms of action.

2) The daily requirement of humans can be estimated, and recommended allowances or "estimated ranges of safe and adequate intakes" have been established (*11*).

3) Although pronounced deficiencies in the free-living population of the United States are very rare, dietary surveys have shown that average intakes far below the recommendations for copper and zinc are quite common in the U.S. population (*33*). Intakes of chromium and selenium range from adequate to marginal, depending on country and region (*16, 25*).

4) The important question remains whether marginal deficiencies, difficult to diagnose for any of the four elements, occur to any substantial degree and present a risk to the health of people. Valid experimental data show that zinc is required not only for growth and development but also for tissue repair and immuno reactions (*34*) and that selenium protects animals against chemically or virally induced malignant tumors (*35*). Both chromium and copper influence recognized risk factors for cardiovascular disease in experimental animals (*26, 36*). The question about marginal deficiencies can be answered only by long-term, prospective studies of population groups that are at risk.

5) The adequacy of the dietary intake is difficult to assess for all four elements because the biological availability of each differs among foods and because the numerous interactions among the elements and with other dietary components are difficult to quantify. For example, foods of animal origin are better sources of chromium and zinc than food of vegetable origin; the opposite is true for selenium. Vitamin C enhances the biological availability of iron, depresses that of copper and, in vitro, renders selenium nearly totally unavailable. These and many additional interactions complicate the task of assessing, even superficially, the adequacy of trace element intakes of individuals or population groups. They also point out the danger of creating new imbalances by self-supplementation with vitamin or trace element preparations.

6) No sensitive diagnostic assays are available to assess marginal nutritional status for these four trace elements, in contrast to the sensitive and reliable methodology for iron and iodine.

The nutritional and public health problems of the trace elements at the second stage of research can be summarized as follows: Severe deficienies can be recognized from clinical signs and remedied. The main nutritional problem in developed countries is the recognition of marginal deficiencies, definition of their consequences, and, if necessary, their prevention. Progress will depend on the development of sensitive diagnostic procedures.

Silicon. Although silicon had been known as a regular constituent of biological materials since the beginning of the century, 90 years passed between the prophecy of Louis Pasteur "effects of silicic acid are destined to play a great and major role in therapy" [cited in (*37*)] and the first demonstration that strongly suggested that silicon may have an essential biological function. Carlisle (*38*) demonstrated by electron microprobe analysis that silicon accumulates to concentrations of 0.5 percent in a narrow zone of ossification of bone, exceeding the concentration of calcium by tenfold. In the more mature zones of the bone with beginning calcium deposition, the silicon concentration sharply decreases again. Subsequently, proof of essentiality for silicon was independently established by two investigators in chicks (*39*) and rats (*40*). The investigators used similar methods, a controlled environment protecting against environmental trace element contamination, and highly purified diets in which the protein requirement was furnished by individual amino acids. Their findings were also similar: both species responded to supplementation with sodium metasilicate (500 μg/g in the diet) with a 30 to 50 percent growth stimulation and both developed severe bone deformities, particularly of the skull, when raised on the silicon-deficient diet. Silicon supplementation, in addition to stimulating growth, maintained normal bone structure. Thus, silicon can be considered an essential trace element.

The mechanism of action of silicon is not yet known, but three potential sites

of action have been suggested (*37, 41*). Silicon is present in high concentrations in mucopolysaccharide-rich tissues, and a proportion of the total amount of the element is bound so tightly that it can be hydrolyzed only by strong acid or alkali treatment. As the most pronounced effect of experimental deficiency is a reduction of the glycosaminoglycans in cartilage, a possible role of silicon in these structures has been suggested. Silicon also occurs in high concentrations and in part firmly bound in collagen, and collagen concentrations in bone are depressed in silicon deficiency. An early hypothesis of a general cross-linking function of silicon in collagen on the basis of one atom of silicon per alpha chain was later revised when it had become obvious that the analytical data on silicon were erroneous, but a cross-linking function at a few, specific sites would still be compatible with more recent analytical data (*37*). Finally, silicon is specifically concentrated in the mitochondria of the bone-forming cells, the osteoblasts. While in the whole cells calcium to silicon ratios are approximately 5 to 1, the silicon concentration within the mitochondria exceeds that of calcium (*41*).

The requirement of chicks and rats for soluble silicon has not been quantified; it is probably between 1 and 100 μg per gram of diet. The requirement of man is also unknown and nutrient composition data for silicon are few and unreliable. Furthermore, it can be predicted that silicon will present many problems of biological availability, depending on dietary source. Despite this lack of reliable nutritional information a protective role of silicon against cardiovascular diseases has been postulated, in part on the basis of negative correlations between the silicon content of water in Finland and the incidence of cardiovascular diseases (*37*), the substantial decline of silicon concentrations in atheromatous aorta tissue, and the results of animal experiments suggesting that silicon, administered to animals on an atherogenic diet, helps preserve the structural integrity of the aorta (*41*).

Silicon was discussed as an example of trace elements in the third stage of research that also include vanadium, nickel, and arsenic. All these elements were postulated to be essential during the past decade, their basic mechanisms of action have yet to be defined, their deficiencies are difficult to induce, and their roles in human nutrition are unknown (*42*). A practical role in humans of any of these can neither be predicted nor excluded. In the developed, industrialized societies the exposure of humans to trace elements from diet and environment has changed during this century, and the change can be expected to continue. Furthermore, many of our chronic diseases of major public health importance are of unknown or of suspected multifactorial origin, and theories on their etiology are open to new ideas that might involve any of the new trace elements. Such ideas, however, must be based on knowledge of their basic mechanisms and sites of action, of human requirements for these elements, and on the definition of nutritional status in man.

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